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**RE: FIFRA 6(a)(2) & TSCA 8(e): Active Ingredient – Zinc Pyrithione  
Preliminary Results Following Dermal Application for 28-Consecutive  
Days.**

Arch Chemicals, Inc. is in the process of evaluating zinc pyrithione in a 28-Day Dermal Neurotoxicity Study in the rat. Based on the preliminary data from this testing the following information is being submitted for your review under the provisions and specifications of FIFRA 6(a)(2) & TSCA 8(e). The compilation of data from the 28-Day Dermal Neurotoxicity Study is not complete and the information that follows is raw unaudited data and is the only data available at this time. On March 24<sup>th</sup>, 2003 Arch Chemicals, Inc. became aware of unaudited draft data from the neurotoxicity study that included electrophysiology and functional endpoints in Sprague -Dawley rats exposed to zinc pyrithione. Previously (October 2001), Arch submitted information based on effects observed at 100 mg/kg via dermal administration as part of an Absorption, Distribution and Excretion study (in progress). The most recent results although not considered a "substantial risk", do constitute new information following dermal application of 50 mg/kg/day in the rat.

The new information obtained from the 28-day neurotoxicity study following dermal application, are summarized below:

**28-Day Neurotoxicity Study via Dermal Exposure:**

A common finding when conducting repeated oral administration studies in rodents is hindlimb weakness. The effect of hindlimb weakness appears to be a unique finding in the rodent (with the rat being the most sensitive species) and rabbit and has not been observed in any other species tested which includes longer term primate studies where primates were exposed to 30-50 times the dose administered to rodents. Previously, studies conducted by Arch Chemicals, Inc. (MRID #42827902) following dermal application of 10, 100, or 1000 mg/kg 5-days/week for 13 weeks failed to produce any signs of hindlimb weakness at any level of exposure. However, It has been shown that administration of zinc pyrithione Monday thru Friday (5-days/week) with no dosing over weekends provides enough of a recovery for the effect of hindlimb weakness not to be manifested. It has been demonstrated that pyrithione-induced hindlimb weakness is reversible, and cessation of exposure results in affected animals returning to a clinically normal state within 7-10 days.

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This study was designed to evaluate the effects of dermal application of zinc pyrithione as dermal exposure is a potential route of exposure. The study incorporated a sensitive electrophysiological technique that measures the evoked compound muscle action potential (CMAP), as measured from the extensor muscle of the tarsus after stimulation of the sciatic nerve. A decrement in the amplitude of the muscle potential has been shown previously to provide a sensitive correlate for muscle weakness following oral administration of zinc pyrithione following 7-10 days of consecutive oral exposure to zinc pyrithione in the diet.

*Study Design for 28-Day Dermal Neurotoxicity Study:*

Twenty Crl:CD®(SD)IGS BR VAF/Plus® male rats were randomly distributed into 4 dose groups with 5 animals per dose. Males were exposed to 0 (vehicle), 50, 150, and 200 mg/kg/day with a dose volume of 1 mL/kg adjusted daily on the basis of body weight. Thirty nonpregnant Crl:CD®(SD)IGS BR VAF/Plus® female rats were assigned to 6 dose groups with 5 animals per dose group. Females were exposed to 0(vehicle), 10, 25, 50, 75, and 100 mg/kg/day. The vehicle was 0.1% triethanolamine-lauryl sulfate (TEALS) in water. TEALS was utilized in order to more evenly disperse the insoluble zinc pyrithione for dermal application. Test article was administered via the dermal route and the treatment site was protected by a convex piece of plastic shielding (holes were drilled into the shielding to minimize hydration of the skin) and the shielding was held in place via a single layer of 3M Micropore™ tape followed by a single layer of Vetrap™ bandaging tape.

Muscle tone was evaluated in the animals on days 0 (just prior to dosing), 4, 8, 11, 15, 18, 22, 25 and 28; forelimb and hindlimb grip strengths were monitored on days 0 (just prior to dosing), 14 and 28; 5 male and female rats in each dose group were selected for cholinesterase assay on days 1, 11, and 28 of study. On day 30 of the study, electrophysiological measurements were recorded for all males in the 0 (vehicle), 50 and 150 mg/kg/day groups and for female rats in the 0 (vehicle), 10, 25, 50 and 75 mg/kg/day dosage groups.

**Results:**

**Male Animals:**

Low muscle tone was observed at 150 and 200 mg/kg/day in male animals beginning on day 8 and day 11 that continued throughout the study duration. Hindlimb and forelimb grip strength was observed to be decreased on days 14 and 28 for male animals receiving 150 and 200 mg/kg/day as were corresponding decreases observed in muscle tone evaluation at the 150 and 200 mg/kg/day dose groups. A decrease in body weight gain and body weight was observed in the 150 and 200 mg/kg/day dose groups. No significant changes in plasma, RBC or brain cholinesterase was observed at any dose tested for any time point measured. Decreases in the electrophysiological measurements measured as the maximum amplitude were observed in males in the 150 mg/kg/day dose group.

**Female Animals:**

In female animals low muscle tone was observed at 50, 75 and 100 mg/kg/day beginning on day 8 in the 100 mg/kg/day dosed group, day 15 in the 75 mg/kg/day group and days 22-28 at the 50 mg/kg/day dosed group. On day 14 grip strength was reduced in the 75 and 100 mg/kg/day dose group and on day 28 grip strength was reduced in the 50, 75, and 100 mg/kg/day dosed groups. No consistent decreases or dose dependent changes were apparent in plasma, RBC or brain cholinesterase values at any dose tested in female animals. Decreases in the electrophysiological measurements measured as the maximum amplitude were observed in the 50 and 75 mg/kg/day doses animals (electrophysiological measurements were not taken at the 100 mg/kg/day dose level).

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**Discussion:**

While the finding of hindlimb weakness, as stated earlier, is unique to the rodent and rabbit, the observation of a decrement in the CMAP amplitude in conjunction with reduced muscle tone (hindlimb weakness) in female rats dosed at 50 mg/kg dermally for 28-consecutive days constitutes new information. Again, as previously stated, an earlier dermal study conducted in the same strain of rat failed to see any effects on the hindlimb clinically or pathologically. The main differences between the 2 studies were the dosing regimen and the dosing vehicle. In the earlier study the animals were dosed 5-days a week for 13-weeks, and in this study the animals were dosed for 28-consecutive days.

Arch Chemicals does not consider this new information as a "*substantial risk*" in light of previous risk assessments carried out by OPPTS scientific staff, which used dermal penetration values for zinc pyrithione at 3-6%. This new data suggests a value in the range of 2-3% for dermal penetration. Also, This effect appears to be unique to the rodent and rabbit and has never been observed in longer term studies conducted at significantly higher doses in primates. When this report becomes finalized it will be forwarded to OPPTS for review.

If you have any questions or require additional information please contact me.

Sincerely,



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